Animal Models of Stroke: Are They Relevant to Human Disease?

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Scientists have been modeling ischemic stroke in animals for over 150 years and have devised many ingenious methods to try to mimic the human condition. Nevertheless, the task remains formidable, even for the most talented scientist utilizing the most sophisticated technology. The challenge would be exceedingly difficult, even if we already understood all the pathophysiology underlying human stroke. While the use of these experimental models has provided much information about the methods of producing and potentially treating cerebral ischemia and infarction in specific animal species and experimental circumstances, the relevance of most of these data to the human condition remains dubious.

Pulsinelli and Buchan recently pointed out that although animal models of cerebral ischemia have been used extensively to test new therapies in human stroke, their record for identifying clinically effective drugs has been disappointing. They noted 25 different compounds of "proven" efficacy for treating focal and global brain ischemia in animal models over the past 10 years based on published articles in refereed journals. Among those compounds subjected to clinical trials, none has proven efficacious, nor have any of these agents come into general clinical use.

To explain the failure of the pharmacologic studies to translate from the animal model to the clinical setting, the authors point to "inexperience and scientific frailties" of the investigators and "weak experimental design and technique," including lack of historical controls, inadequate numbers of animals to rule out Type II errors, inadequate physiological monitoring, inappropriate histological analysis, and lack of control over reproducibility of the ischemic insult.

In a similar commentary, Molinari eloquently summarized the rationale for using animal stroke models in stroke research, pointing out several advantages including the uniformity of the models, the quantitative gradation of the ischemic insult in certain models, and, in general, the quantifiable pathologic outcomes. However, he too points out several therapies for acute stroke which have proven effective in reducing lesion size in animal models while being clinically ineffective in humans. To explain this lack of correlation between animal studies and the human condition, he points to the lack of clinical pathologic correlation in humans and concludes that "unless we use analytic methods in the clinical tests in humans similar to those used in the animal models originally suggesting the efficacious treatment, we are destined to repeat the now familiar and recurrent sequence."

We would like to offer a different perspective about the use of animal models for human stroke and some reasons why an over-reliance upon such models may impede rather than advance scientific progress in the treatment of this disease.

The complexities of creating a truly representative model for human ischemic stroke go far beyond developing ways to occlude a cerebral artery in a given animal. A large proportion of patients with ischemic stroke have underlying multifocal atherosclerosis which has developed over many years or decades. Such individuals may have numerous associated risk factors which predispose to this disease process, including genetic factors, chronic hypertension, diabetes mellitus, and cigarette smoking. Many patients are taking one or more prescribed drugs that may affect the ischemic process or interact with a proposed therapeutic intervention. Each of these variables may have important independent effects upon the ultimate outcome or response to therapy in humans. Some attempts have been made to model atherosclerosis in some animal species and to account for hypertension and increasing age, but it is clear that these circumstances do not reproduce the human situation. In fact, most models of ischemic stroke are derived from very young animals with no underlying chronic disease or any genetic predisposition to such diseases. Many variations, both within and between species, have been recognized, not only in the vascular anatomy, but also in histopathologic responses to identical ischemic insults and treatment responses to cerebral ischemia.
Despite even the best technical efforts by researchers, there are some difficulties with the techniques themselves. With some ligation techniques, craniotomy introduces several variables unlike the human disease situation. These include skull trauma, external blood vessel injury, and changes in intracranial pressure.\textsuperscript{11,12} While most of the embolic techniques avoid the invasive features of craniotomy, they provide less control over the location and extent of the resulting cerebral infarction. Foreign body techniques also fail to mimic many observable features of human emboli, including the tendency for human clots to undergo lysis, migrate into distal portions of the arterial system, or recanalize over time.\textsuperscript{13}

Another confounding variable in experimental strokes involves the use of general anesthesia, which is desirable for humane reasons. However, anesthesia produces a state of altered metabolic demands by the brain, and changes in several metabolic parameters may vary with different anesthetic agents in different species.\textsuperscript{14} For this reason, in recent years there has been a tendency to avoid general anesthesia when possible in stroke models, but this introduces animal stress, another undesirable variable, which has the potential for altering other parameters, including release of endogenous corticosteroids.\textsuperscript{15}

It is also difficult to assess the clinical condition of animal subjects after an experimental stroke has been induced or treatment attempted, and anesthesia further confounds this assessment. Several important components of the neurological examination cannot be adequately tested in most animals, and some components are inaccessible, such as language and other cognitive functions.

Given these formidable obstacles to modeling the human situation, it is hardly surprising that the correlation between studies involving animal models and human patients would be less than perfect. In fact, as Molinari\textsuperscript{2} has pointed out, we have been repeating a familiar and recurrent sequence of continuing to "renew hope through the experimental neuropathology of animal modeling, only to be disappointed by the results of large-scale, statistically valid clinical trials that are not designed to measure comparative neuropathology in humans."

Each time one of these potential treatments is observed to be effective based upon animal research, it propagates numerous further animal and human studies consuming enormous amounts of time and effort to prove that the observation has little or no relevance to human disease or that it may have been an artifact of the animal model itself.

Barbiturate treatment is a relevant example which, in models of global and focal ischemia in animals, was associated with relative or complete protection from cerebral infarction in several studies.\textsuperscript{16-20} Over the past 10 years, it has gradually become clear that barbiturates have little or no protective effect in humans,\textsuperscript{21} and some investigators\textsuperscript{20} have hypothesized that the mechanism of action of barbiturates in animals may be through its anticonvulsant effect.

Another recent example of a compound that has been extensively tested in several species of animals with "promising results" is MK-801. Even though protective effects have been shown when this drug was administered before focal and generalized cerebral ischemia, the clinical relevance of utilizing treatment agents prior to cerebral ischemia must be very limited. Graham et al\textsuperscript{22} recently showed a reduction in the amount of structural brain damage when MK-801 was given 2 hours after MCA occlusion in the cat and 30 minutes after MCA occlusion in the rat. However, given that the animals were killed at 6 hours (cat) or 3 hours (rat) after MCA occlusion, it is unclear whether treatment with MK-801 would ultimately result in reduced infarct volume or whether the treatment was merely delaying the manifestation of infarction. Even in the human, this end point may have little or no relevance to clinical outcome.

There have also been major discrepancies in the effects of MK-801 on different species of animals. Graham et al\textsuperscript{22} reported a consistent but transient increase in mean arterial blood pressure in cats treated with MK-801 compared to marked sustained hypotension in rats treated with this agent. Shearman\textsuperscript{10} cited gross differences in the protective effect of MK-801 between the dog and primate. With such major discrepancies in physiologic and therapeutic effects among various species of animals, it should not be surprising that a similar discrepancy might well exist between any of these species and humans.

In his editorial, Molinari\textsuperscript{2} suggested we modify measurement of human outcomes to conform to animal research so that we can reproduce the results of the animal research in humans. We suggest the converse, namely that there is a great need to design experimental projects and therapeutic interventions in such a way that they have relevance and practical application to the human condition. After all, the primary goal of animal research is to improve healthcare beyond the laboratory. We propose that clinical outcome measures are ultimately the only relevant measures of success for stroke treatment. If minor quantitative improvements in CT scans, MRI scans, or any other laboratory parameter occur without any accompanying clinical improvement, one can hardly conclude that the treatment has "great promise."

We assert that the discrepancies between animal research observations and those in humans will not disappear by developing ways of improving clinical research. Although clinical research may well have much room for improvement, the discrepancies are rooted primarily in the challenging task of modeling human disease and assessing relevant measures of therapeutic efficacy in animals.

Although the use of animals will continue to contribute substantially to research in stroke for the foreseeable future, the greatest potential lies in the study of molecular mechanisms in the pathophysiology of ischemia and the variables that affect extension and reversibility of the territory of ischemic
injury. There is also no current alternative to animal studies of safety and effect in the screening of agents that may benefit patients with stroke. Ultimately, however, the answers to many of our questions regarding the underlying pathophysiology and treatment of stroke do not lie with continued attempts to model the human situation perfectly in animals, but rather with the development of techniques to enable the study of more basic metabolism, pathophysiology, and anatomical imaging detail in living humans.

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